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Original Article

Sleep-disordered breathing does not affect nocturnal dipping, as assessed by pulse transit time, in preschool children: evidence for early intervention to prevent adverse cardiovascular effects? ☆

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ABSTRACT

Objective: Sleep-disordered breathing (SDB) is associated with reduced nocturnal dipping of blood pressure (BP) and sleep disruption in adults, and these features confer an increased risk of cardiovascular events. As SDB prevalence in children peaks during the preschool years, we investigated nocturnal dipping and sleep fragmentation in preschool children with SDB.
Methods: Children (3–5 years; $n = 163$) grouped by obstructive apnoea hypopnoea index (OAHI): control, no snoring history and OAHI $\leqslant$1 event/h; primary snoring, OAHI $\leqslant$1 event/h; mild SDB, >1–$\leqslant$5 events/h; moderate–severe SDB, >5 events/h. Pulse transit time (PTT), an inverse continuous indicator of BP changes, and heart rate (HR) during total sleep time and the first period of rapid eye movement (REM), non-REM (NREM)1/2 and NREM3/4 sleep were expressed as percentage change from wake before sleep onset. The sleep fragmentation index (SFI) was calculated as the number of sleep stage transitions or awakenings per hour of sleep.
Results: There were no group differences in the change in PTT or HR from wake to total sleep time or to individual sleep stages or in the proportion of children in the quartile with the smallest change in PTT during total sleep. Children with moderate–severe SDB had higher SFI than primary snoring (PS) or mild SDB groups ($p < 0.05$ for both) and controls ($p = 0.07$).
Conclusions: In contrast to adults, nocturnal dipping is preserved in young children with SDB, despite increased sleep fragmentation. As there is evidence that nocturnal dipping is similarly preserved at the school age, childhood may pose a window of opportunity for resolution of SDB when the cardiovascular effects are less marked.

1. Introduction

Nocturnal blood pressure (BP) is considerably lower than daytime levels, a phenomenon known as 'nocturnal dipping' [1]. The loss of this normal decline (a nocturnal decrease in BP of <10%) is termed 'non-dipping' [1,2]. Through epidemiological studies in adults, reduced nocturnal dipping has been associated with poorer outcomes, in particular, an increased risk of future cardiovascular events [3–7]. Furthermore, the degree of nocturnal dipping has been related to sleep quality, with deeper and less fragmented sleep being associated with greater BP dipping in healthy adults [8]. In adults with obstructive sleep apnoea (OSA), this typical fall in BP with sleep is significantly reduced or even absent [9–14].

The spectrum of disorders commonly referred to as sleep-disordered breathing (SDB) is a relatively common childhood disease. While OSA forms the severe end of SDB, affecting 1–5% of children [15], primary snoring (PS) comprises the mild end of the continuum and affects a significant number of children (3–15%) [16]. A number of studies have found significant and clinical effects of all severities of SDB, including PS on the cardiovascular system [17–20]. However, studies investigating nocturnal dipping patterns

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in school-aged children with SDB have thus far yielded conflicting results, with some having reported reduced nocturnal dipping [21–23], preserved dipping [24,25], or a reduction in dipping only in the group with the most severe OSA [18]. The majority of these studies have calculated nocturnal dipping from intermittent ambulatory BP monitoring [18,21–24], the limitations of which include possible sleep disruption [26] and the inability to assess transient BP changes and the effects of sleep state due to the small number of measurements that are able to be made across the night. Recently, our group used a continuous method of BP measurement and accounted for the effects of sleep state in children aged 7–12 years [25]. Whilst both SDB severity group and sleep state affected absolute BP levels, no differences were found between the proportion of children who exhibited nocturnal dipping in each SDB severity group or between sleep states. Unlike adults with SDB, children with SDB generally exhibit normal sleep architecture [27]. However, indices of sleep fragmentation have been shown to distinguish school-aged children with and without SDB; children with SDB exhibited a greater number of sleep-stage changes and a shorter mean contiguous duration of NREM2 sleep [28].

Despite the peak prevalence of SDB occurring at the preschool age, when the size of the adenotonsillar tissue is largest in comparison to the surrounding structures [29], the impact of SDB on nocturnal dipping in young children has not been addressed. Devices that continuously measure BP, such as the Finometer™ used by our group previously [25], are not appropriately sized for preschool-aged children. An alternative surrogate method of continuous and non-invasive assessment of changes in BP is pulse transit time (PTT). Through non-invasive beat-to-beat measurement of the time taken for the arterial pulse pressure wave to travel from the left ventricle to a predetermined peripheral site, PTT is inversely correlated with changes in BP. The degree of stiffness of the arterial wall, which is highly dependent on the instantaneous BP, is the main determinant of the time that the arterial pulse pressure wave takes to reach the periphery. Thus, an increase in PTT is suggestive of a fall in BP [30,31], which occurs nocturnally. Initially studied in adults, PTT showed a high inverse correlation with intra-arterial BP of between $r = -0.91$ and -0.98 [32]. Similarly, inverse correlations between PTT and clinically used cuff-based BP measurements have been reported in both normotensive [30,33] and hypertensive children [34]. More recently, PTT has been used in children to detect physiological BP changes in a number of situations [35–38].

In this study, we examined nocturnal dipping patterns and sleep fragmentation in preschool children with a range of SDB severities and non-snoring control children. We hypothesised that in comparison to non-snoring control children, children with SDB would exhibit (i) a smaller change in PTT from wake to sleep, suggesting decreased nocturnal BP dipping and (ii) greater sleep fragmentation. Furthermore, we hypothesised that the degree of nocturnal dipping would be inversely proportional to both the severity of their SDB and their sleep fragmentation.

2. Methods

2.1. Subjects and study protocol

The current study formed part of a larger study investigating the cardiovascular and neurocognitive effects of SDB in preschool children, of which results of neurobehavioural [39], quality of life [40], sleep pressure and homeostasis [41,42] and overnight effects of sleep stage on PTT changes (suggesting BP changes) [35] have been published. Ethical approval was granted by the Southern Health and Monash University Human Research Ethics Committees and procedures followed were in accordance with institutional guidelines. Written informed consent was obtained from participants' parents, following a full explanation of the procedure. No monetary incentive was given for participation. Children, aged 3–5 years, referred to the Melbourne Children's Sleep Centre for assessment of suspected SDB between July 2008 and May 2011 were recruited. Control children of the same age with no history of snoring were recruited from the community. Children with conditions or taking medications known to affect sleep, breathing, BP or neurocognitive function were not recruited. All children were otherwise healthy. Height and weight were measured and converted to a body mass index (BMI) *z*-score to adjust for gender and age [43]. Office BP was taken in triplicate during restful wakefulness, sitting upright, using an electronic BP monitor (Dinamap V100, CARESCAPETM, Freiburg, Germany) and an appropriately sized cuff. Systolic and diastolic blood pressure (SBP, DBP) measurements were converted to *z*-scores relative to age, gender and height [44].

All children underwent routine overnight polysomnography (PSG), the full details of which have been previously published [35,39,41,42]. Briefly, this involved electroencephalogram (C4–A1, C3–A2 with O2–A1 and O1–A2 if $\geqslant$4 years), submental and anterior tibialis muscle electromyograms, left and right electrooculograms, three-lead electrocardiogram (ECG), respiratory movements, oxygen saturation and measurements of airflow (nasal pressure and thermistor) and transcutaneous carbon dioxide. An additional photoplethysmographic probe (PPG) (Adult Flex Sensor 3M, Nonin Medical Inc., Plymouth, MN, USA) recorded the pulse waveform necessary for PTT analysis. ECG and PPG were sampled at 512 Hz. PSG recording began before lights out and included wake before sleep onset for a minimum of 10 min in all subjects. Each child was instructed to lie still in the prone position with their hands by their side. This baseline wake recording took place while the child watched television or was read a story by his/her parent.

PSG sleep staging in 30-s epochs [45] and respiratory event scoring were performed in accordance with international standards at the time of study [46] and have been detailed in our previous publications [35,39–42]. In summary, respiratory events $\geqslant$2 respiratory cycles in duration were scored [46] and the obstructive apnoea hypopnoea index (OAHI) (total number of obstructive apnoeas, mixed apnoeas and obstructive hypopnoeas/h of total sleep time (TST)) was used to define SDB severity groups. PS was defined as an OAHI $\leqslant$1 event/h; Mild OSA as an OAHI >1–$\leqslant$5 events/h; and moderate–severe (MS) OSA as an OAHI >5 events/h. Control children had an OAHI $\leqslant$1 event/h and no snoring was observed during the PSG or reported by parents. Other measures of respiratory disturbance calculated were the respiratory disturbance index (RDI), defined as the number of obstructive, central and mixed apnoeas and hypopneas/h of TST, the arousal index (AI), defined as the number of arousals/h of TST, the oxygen saturation (SpO_2) nadir, defined as the lowest SpO_2 associated with a respiratory event and the 3% oxygen desaturation index (ODI3%), defined as the number of dips in SpO_2 $\geqslant$3% associated with respiratory events/h of TST.

2.2. Data analysis

Following the study, all PSG data were transferred via European Data Format to specialised data analysis software (LabChart 7.2, ADInstruments, Sydney, Australia). Epochs containing wake after sleep onset (WASO) were excluded, together with epochs containing manually identified movement artefact (gross body movement affecting all PSG channels or artefact isolated to ECG or PPG signals). PTT was calculated for each beat in LabChart, using peak detection to identify each peak of the ECG R-wave. The 50% point of the pulse-wave height on the corresponding PPG signal was similarly determined, as this point is most resistant to artefact [30,31].

PTT was calculated beat by beat as the time delay between these two points. To do this, nine channels were calculated offline, in addition to the 16 standard PSG channels recorded during the overnight study. Based upon the ECG and PPG signals, each successive calculated channel identified a subsequent section of the waveforms of interest and measured or calculated specific components necessary for the final PTT calculation. For example, channels measured the height of the minimum and maximum values of each PPG waveform and the fiducial point of each R-wave on the ECG was identified. In other channels, different algorithms were used to detect height, periodicity, changes in polarity in the signal and ultimately the calculation of the PTT. An average PTT was then calculated for each 30-s epoch of wake and sleep. In each child, PTT was first averaged for total sleep over the whole night (excluding wake and movement). Subsequently, the effects of sleep stage during the first sleep cycle were examined, whereby PTT was averaged for the first periods of each of rapid eye movement (REM), non-REM (NREM)1/2 and NREM3/4 in each child. This was defined as the first cluster of three or more contiguous epochs of those specific sleep stages (e.g., NREM1 and NREM2) after sleep onset, interrupted by <3 contiguous epochs of wake or another sleep stage. The first sleep cycle was chosen for analysis to target the point of maximal BP decline, as minimum BP levels have previously been reported in the first 1–2 h of sleep in adults [47,48], which corresponds to the first sleep cycle. This method has also been used to analyse nocturnal dipping of BP in primary school-aged children [49]. In each child, the mean PTT for each period analysed was expressed as the percentage change from that child's mean PTT during wake before sleep onset.

As percentage change in BP is not directly equivalent to percentage change in PTT, division of subjects into 'dippers' and 'non-dippers' as done traditionally (based on a nocturnal fall in BP of greater or less than 10% compared to wake levels [1,2,47]) was not possible in this study. Instead, the total cohort was arbitrarily divided into two groups; the quartile exhibiting the least percentage change in PTT from wake to total sleep (⩽25th percentile) representing the children with the smallest nocturnal fall in BP and who thus were most likely to be non-dippers and the remainder of the cohort (>25th percentile).

The sleep fragmentation index (SFI), defined as the number of sleep stage transitions or awakenings per hour of sleep [50], was calculated for each child. Additionally, contiguous durations were calculated for each individual sleep stage (NREM1, NREM2, NREM3, NREM4 and REM sleep) and WASO as the number of consecutive 30-s epochs scored with the same sleep stage [28], which reflected the elapsed time between two sleep-stage transitions. A mean contiguous duration was calculated for each sleep stage in each child.

2.3. Statistical analyses

Statistical analyses were conducted using SPSS® (IBM® Statistics version 19, Chicago, IL, USA). Data were first tested for normality and equal variance. Group demographic, wake BP *z*-scores and PSG variables, SFI and mean contiguous durations of sleep stages (NREM1, NREM2, NREM3, NREM4 and REM) and WASO were compared using one-way analysis of variance (ANOVA) with Student–Newman–Keuls *post hoc* testing, and Kruskal–Wallis ANOVA on ranks with *post hoc* Mann–Whitney *U*-tests when not normally distributed. General linear model-repeated measures with Bonferroni *post hoc* testing were used to examine the effects of SDB severity group and sleep stages on the percentage change in PTT and heart rate (HR) and on absolute HR. The proportions of subjects found in the quartile of least nocturnal change in PTT in each group were compared using chi-squared analysis. Pearson correlations were performed to assess the relationship between percentage change in PTT and HR from wake to total sleep with BMI *z*-score, OAHI, ODI3%, SpO_2 nadir and SFI. Pearson correlations were performed to assess the relationship between SFI and mean contiguous durations of individual sleep stages and WASO, and between SFI and conventional PSG indices of sleep fragmentation (AI, RDI, sleep efficiency) and SDB severity (OAHI, ODI3%, BMI *z*-score).

3. Results

A total of 192 preschool children (151 cases, 41 controls) were recruited. Children were excluded if they had <4 h of sleep or <5 min of artefact-free PTT data during wake before sleep onset. There were 163 subjects available for nocturnal dipping analysis (35 Controls, 66 PS, 34 Mild OSA and 28 MS OSA) and 179 subjects for sleep fragmentation analysis (38 Controls, 72 PS, 31 Mild OSA, 38 MS OSA).

3.1. Demographic and PSG characteristics

Demographic and PSG characteristics of these subjects have been previously published [35]. In summary, there were no group differences in age, gender, wake BP *z*-scores or traditionally measured sleep efficiency. BMI *z*-score was significantly higher in the Mild OSA group than all other groups ($p < 0.05$ for all). Due to study design, the OAHI and other measures of OSA severity were significantly higher in the MS OSA group compared to the other groups ($p \leqslant 0.01$ for all). There was no group difference in the average transcutaneous carbon dioxide level (mmHg) for total sleep time. The maximum transcutaneous carbon dioxide level (mmHg) for total sleep time was significantly higher in the Mild OSA group compared to the PS group ($p < 0.05$). Both the Mild and MS OSA groups had a significantly higher percentage of total sleep time with the transcutaneous carbon dioxide level >50 mmHg compared with the control group, and the Mild OSA was also higher than the PS group ($p < 0.05$ for all). A summary of subject demographic and PSG variables is shown in Table 1.

3.2. Nocturnal changes in PTT and HR

3.2.1. Effect of SDB severity

Fig. 1 illustrates the change in percentage PTT (A) and HR (B) from wake to total sleep and to the first periods of NREM1/2, NREM3/4 and REM sleep, in the control and SDB severity groups. There was no significant group difference in the percentage change in PTT or HR from wake to sleep in any of the sleep periods analysed. There were also no significant group differences in absolute HR during wake or any of the sleep periods analysed. Absolute HRs for wake, total sleep and the first periods of NREM1/2, NREM3/4 and REM sleep are shown in Table 2.

3.2.2. Effect of sleep and sleep stages

Sleep stage had a significant effect on percentage change in PTT and HR from wake ($p < 0.001$ for both), as shown in Fig. 2A and B, respectively. On average, PTT rose by 8% and HR fell by 14% from wake to total sleep. The change to total sleep was significantly greater than to specific sleep stages ($p < 0.05$ for all) and was significantly less to NREM1/2 than to all other sleep stages ($p < 0.001$ for all). Percentage change in HR from wake to NREM3/4 was greater than to REM sleep ($p < 0.001$); however, percentage change in PTT was similar from wake to NREM3/4 and REM sleep. Similarly, absolute HR was significantly different between all wake and sleep periods analysed ($p < 0.001$ for all).

Table 1
Subject demographic and polysomnographic characteristics.

	Control (n = 35)	PS (n = 66)	Mild OSA n = 34)	MS OSA (n = 28)
Male, n	18	37	24	17
Age, y	4.4 (0.1)	4.3 (0.1)	4.6 (0.1)	4.3 (0.2)
BMI z-score	0.5 (0.2)	0.7 (0.1)	1.2 (0.2)*,†,§	0.4 (0.2)
SBP z-score	0.6 (0.2)	0.5 (0.9)	0.8 (0.2)	0.4 (0.2)
DBP z-score	0.6 (0.1)	0.4 (0.1)	0.6 (0.1)	0.5 (0.2)
Sleep efficiency, %	88.8 (0.9)	87.3 (0.9)	88.2 (1.1)	88.2 (1.4)
RDI, h TST	1.0 (0.1)	2.2 (0.3)*	4.9 (0.4)*,†	16.4 (1.6)*,†,‡
AI, h TST	12.2 (0.7)	12.6 (0.6)	14.3 (0.7)*,†	25.6 (1.6)*,†,‡
OAHI, h TST	0.1 (0.0)	0.3 (0.0)*	2.8 (0.2)*,†	13.5 (1.5)*,†,‡
ODI3%, h TST	0.6 (0.1)	1.5 (0.3)*	2.2 (0.4)*,†	7.0 (1.2)*,†,‡
SpO_2 nadir, %	93 (1)	92 (1)	91 (1)	89 (6)*,†,‡
Av TCO_2 TST, mmHg	44 (1)	49 (4)	46 (1)	44 (1)
Max TCO_2 TST, mmHg	51 (1)	50 (1)	54 (1)†	52 (1)
TCO_2 50, %TST	13 (2)	16 (1)	25 (5)*,†	19 (4)*

Values presented as mean (SEM). AI, arousal index; BMI, body mass index; DBP, diastolic blood pressure; MS, moderate–severe; OAHI, obstructive apnoea–hypopnoea index; ODI3%, 3% oxygen desaturation index; OSA, obstructive sleep apnoea; PS, primary snoring; RDI, respiratory disturbance index; SBP, systolic blood pressure; SpO_2, oxygen saturation; TST, total sleep time; Av TCO_2, average transcutaneous carbon dioxide; TCO_2 50, %TST, the %TST with TCO_2 >50 mmHg.
* $p < 0.05$ versus Control.
† $p < 0.05$ versus PS.
‡ $p < 0.05$ versus Mild OSA.
§ $p < 0.05$ versus MS OSA.

3.3. Quartile with the smallest nocturnal change in PTT

To replace a comparison of 'dippers' and 'non-dippers' based on traditional categorisation, in this study, subjects exhibiting the smallest nocturnal change in PTT were compared to the remainder of the cohort. The 25th percentile of change in PTT from wake to total sleep was 5.5%; hence, subjects with a change in PTT from wake to total sleep of ⩽5.5% made up the quartile with the least change. Fig. 3 shows the subjects in the quartile of least change, presented as a proportion of their SDB severity group. The MS OSA group had the largest proportion of subjects in the quartile with the smallest change (41%), compared to Controls (23%), PS (25%) and Mild OSA (15%) groups. However, there was no statistically significant difference between the proportions of children in the quartile with the smallest dip in each group.

Table 2
Group comparison of absolute HR (bpm) for analysed wake and sleep periods.

	Control (n = 35)	PS (n = 66)	Mild OSA (n = 34)	MS OSA (n = 28)
Wake (before sleep onset)	98 (2)	101 (1)	99 (2)	101 (2)
Total sleep	86 (2)	86 (1)	85 (2)	88 (2)
NREM1/2 (1st period)	92 (2)	94 (1)	94 (2)	96 (2)
NREM3/4 (1st period)	86 (2)	88 (1)	87 (2)	89 (2)
REM (1st period)	91 (2)	91 (1)	89 (2)	92 (2)

Values presented as mean (SEM). HR, heart rate; MS, moderate–severe; NREM, non-rapid eye movement; OSA, obstructive sleep apnoea; PS, primary snoring; REM, rapid eye movement.

3.4. Sleep fragmentation and mean contiguous duration of sleep stages

The SFI for each group is shown in Fig. 4. SFI was highest in the MS OSA group, which was statistically significantly higher in comparison to the PS and Mild OSA groups ($p < 0.05$ for both); however, the values did not reach significance in comparison to the Control group ($p = 0.07$). SFIs in the Control, PS and Mild OSA groups were not different. The mean contiguous duration of each sleep stage and WASO for each severity group is shown in Table 3. The mean contiguous duration of NREM1 sleep was significantly different between group overalls ($p = 0.04$), although *post hoc* testing could not identify where the difference lay and the actual group differences were very small. The mean contiguous durations of both NREM3 and NREM4 sleep differed significantly between groups; control children had significantly smaller bouts of NREM3 sleep than all SDB groups ($p < 0.05$ for all), and significantly longer bouts of NREM4 sleep compared to all SDB groups ($p < 0.05$ for all). There were no group differences in the mean contiguous durations of NREM2, REM sleep or WASO.

3.5. Correlates of sleep fragmentation and changes in PTT and HR

Percentage change in HR from wake to total sleep was weakly correlated with OAHI ($r = 0.17$, $p = 0.03$), ODI3% ($r = 0.24$, $p = 0.003$) and SpO_2 nadir ($r = -0.16$, $p = 0.04$); however, percentage change in PTT was not correlated with any index of SDB severity. To overcome the effect of multiple subjects having an OAHI of zero, the correlations between percentage change in PTT and HR from wake to total sleep and OAHI, ODI3% and SpO_2 nadir were repeated in children with OSA only (OAHI >1 event/h). In that analysis, percentage change in PTT was correlated with SpO_2 nadir ($r = 0.27$, $p = 0.03$) but not OAHI or ODI3%; percentage change in HR was still weakly correlated with ODI3% ($r = 0.36$, $p = 0.01$)

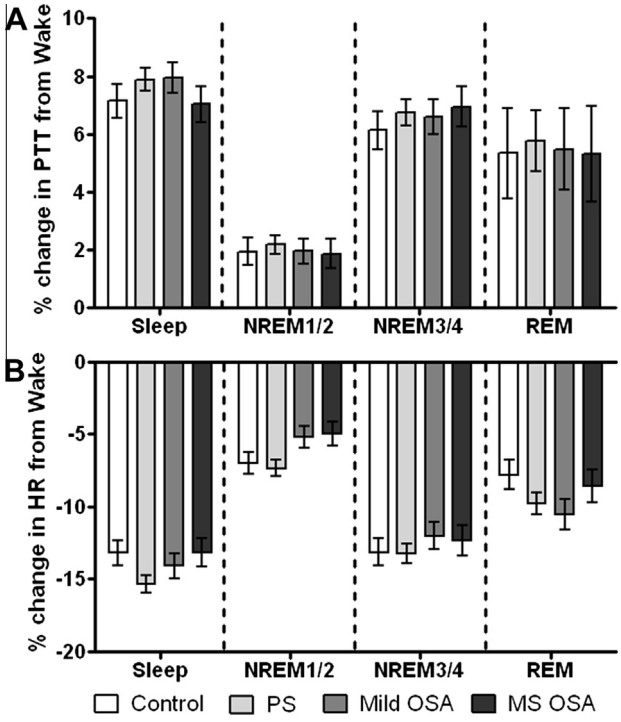

Fig. 1. Group comparison of the % change in PTT (A) and HR (B) from wake to total sleep and to the first periods of NREM1/2, NREM3/4 and REM sleep. PTT, pulse transit time; PS, primary snoring; OSA, obstructive sleep apnoea; MS, moderate–severe; NREM, non-rapid eye movement; REM, rapid eye movement. Wake denotes wake before sleep onset. Data presented as mean ± SE.

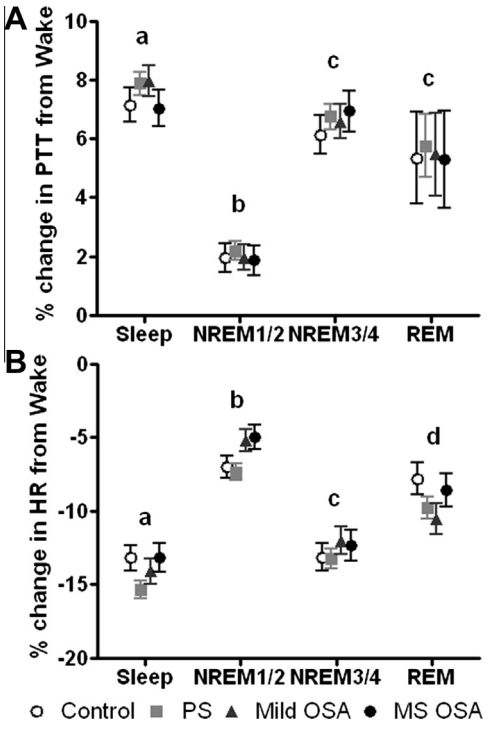

Fig. 2. Sleep stage comparison of the % change in PTT (A) and HR (B) from wake to total sleep and to the first periods of NREM1/2, NREM3/4 and REM sleep, in each of the control and SDB severity groups. PTT, pulse transit time; PS, primary snoring; OSA, obstructive sleep apnoea; MS, moderate–severe; NREM, non-rapid eye movement; REM, rapid eye movement. Note the *y*-axis of negative change in HR (B) whereby greater change is closer to the *x*-axis. Wake denotes wake before sleep onset. Data presented as mean ± SE. Sleep stages that do not have a letter in common significantly different ($p < 0.05$).

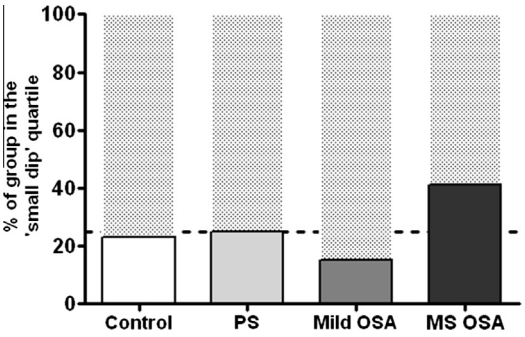

Fig. 3. Subjects found in the quartile with the smallest change in pulse transit time from wake to total sleep, expressed as a percentage of their respective group. Broken black line indicates 25% mark of each group. PS, primary snoring; OSA, obstructive sleep apnoea; MS, moderate–severe.

and SpO_2 nadir ($r = -0.31$, $p = 0.01$); however, the correlation with OAHI no longer reached significance ($r = 0.24$, $p = 0.06$). Percentage change in PTT or HR from wake to total sleep was not correlated with BMI *z*-score or SFI. SFI was correlated with the mean contiguous duration of NREM1 ($r = -0.17$, $p = 0.04$), NREM2 ($r = -0.74$, $p < 0.001$), NREM3 ($r = -0.17$, $p = 0.03$), NREM4 ($r = -0.4$, $p < 0.001$) and REM ($r = -0.36$, $p < 0.001$) sleep, but not WASO. SFI was weakly correlated with RDI ($r = 0.18$, $p = 0.02$) and OAHI ($r = 0.19$, $p = 0.01$) and strongly correlated with AI ($r = 0.42$, $p < 0.001$). SFI was not correlated with BMI *z*-score, sleep efficiency or ODI3%.

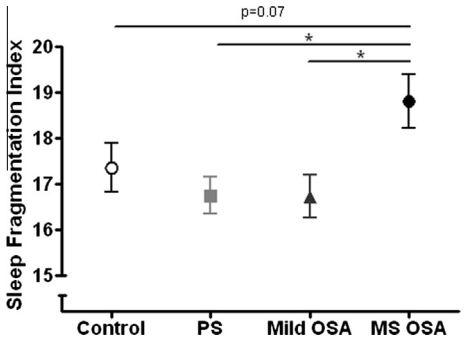

Fig. 4. Sleep fragmentation index (number of sleep stage shifts or awakenings per hour of sleep) in the control, primary snoring (PS), mild obstructive sleep apnoea (OSA) and moderate–severe (MS) OSA groups. Data presented as mean ± SE. $^{*}p < 0.05$.

4. Discussion

This is the first study to evaluate nocturnal dipping of BP (as suggested by an increase in PTT) and HR specifically in preschool-aged children with SDB and furthermore consider the findings in the context of sleep fragmentation. The increase in PTT from wake to sleep suggests a nocturnal decline in BP, which was of a similar magnitude in children with all severities of SDB when compared with non-snoring control children. These results suggest that nocturnal dipping is preserved in young children with SDB, irrespective of severity and despite those with MS OSA having more fragmented sleep.

Compared to waking levels, we observed a reduction in HR and an increase in PTT during total overnight sleep, which suggests a nocturnal decline in BP and HR in our preschool-aged children. This is consistent with numerous previous studies in older children that showed a change in BP and HR from wake to sleep, both in children with [18,21–24,51–53] and without [54–56] SDB. Additionally, we found that in all groups of children, PTT increased and HR decreased from wake to each of the first periods of NREM1/2, NREM3/4 and REM sleep. Of these sleep stages, the greatest increase in PTT and reduction in HR was seen during NREM3/4 sleep, although the magnitude of change was less than what was demonstrated across the entire night of sleep. Few studies have reported dipping patterns specific to sleep stage in children and have largely reported no differences in the degree of dipping from wake to NREM or REM sleep [23,25,52,53]. However, our differences between sleep stages are not unexpected. In adults, BP gradually decreases in the first 1–2 h of sleep in parallel with the deepening stages of sleep, reaching a nadir in NREM3/4 sleep [57]. In this cohort of preschool children with and without SDB, we have previously reported that when measured over the entire night of sleep, PTT is highest during NREM sleep [35], suggesting the lowest levels of BP. The present study results pertain to the first period of the night for each sleep state, a period chosen to target the point of maximal BP decline [47,48]. The differing results of sleep state between the present study and other studies that measured ambulatory BP may be explained by the frequency of measurements, as ambulatory BP studies obtain only intermittent measurements and furthermore can induce arousals thereby artificially increasing the BP [26]. In the present study, nocturnal dipping was calculated as percentage change from restful wake before sleep onset, whereas many studies report 24 h ambulatory BP measurements [1]. It is likely that a greater percentage change would have been observed had we recorded over a 24 h period; however, as both control children and those with SDB were subject to the same protocol, it is likely that the same pattern of results would have been obtained. This method of using BP during resting wake before sleep

Table 3
Group comparison of mean contiguous duration in minutes of WASO and each sleep stage.

	Control (n = 38)	PS (n = 72)	Mild OSA (n = 38)	MS OSA (n = 31)
WASO contiguous duration, min	2.0 (0.3)	2.0 (0.2)	1.9 (0.2)	1.9 (0.3)
NREM1 contiguous duration, min	1.2 (0.1)	1.3 (0.1)	1.4 (0.1)	1.4 (0.1)
NREM2 contiguous duration, min	5.0 (0.2)	5.4 (0.2)	5.4 (0.2)	4.7 (0.2)
NREM3 contiguous duration, min	0.9 (0.1)	1.1 (0.1)*	1.1 (0.1)*	1.2 (0.1)*
NREM4 contiguous duration, min	20.4 (1.1)	15.9 (1.0)*	16.3 (1.6)*	13.3 (0.9)*
REM contiguous duration, min	9.2 (0.8)	10.0 (0.5)	10.5 (0.6)	9.4 (0.7)

Values presented as mean (SEM). MS, moderate–severe; NREM, non-rapid eye movement; OSA, obstructive sleep apnoea; PS, primary snoring; REM, rapid eye movement; WASO, wake after sleep onset.
* $p < 0.05$ versus Control.

onset to study nocturnal dipping has been used previously in both adults [58] and by ourselves in older children [25].

Preschool children with all severities of SDB had shorter average durations of uninterrupted NREM4 sleep than non-snoring children. This difference was greatest in the MS OSA group, which demonstrated that contiguous periods of NREM4 sleep were, on an average, 7 min shorter per period than for control children. Furthermore, increased sleep fragmentation, reflecting a greater proportion of overnight sleep stage transitions and short periods of awakening, was seen in the children with MS OSA. The SFI, calculated as the number of sleep stage transitions or awakenings per h of sleep, is reflective of sleep quality and consolidation. Whilst the numerical value itself is not clinically meaningful, it is rather the comparison between groups that is of interest. In essence, it is a numerical representation of the hypnogram, which can be used as an adjunct to other measures of sleep macrostructure, such as percentage of total sleep time in each sleep stage. The SFI has been correlated with other measures of sleep discontinuity, such as the micro-AI, percentage of WASO, apnoea–hypopnoea index and ODI3% [44]. However, we did not find a graded response of increasing sleep fragmentation with increasing severity as we had hypothesised, rather we found sleep fragmentation in children with PS and mild OSA to be no different from that in non-snoring children. We found that children with PS, mild and MS OSA had similar mean length of NREM4 sleep periods; however, mean duration was significantly longer in control children compared with all SDB groups. These findings perhaps warn against using one marker alone to indicate sleep fragmentation; alternatively, they demonstrate that whilst children with milder forms of SDB (PS, mild OSA) do not exhibit an increased number of sleep stage transitions, that is, do not exhibit increased sleep disruption, they do however demonstrate an inability to preserve their uninterrupted NREM4 sleep. In our preschool cohort, sleep fragmentation was not related to the nocturnal change in PTT and HR over the whole night. This is similar to a study of adults with OSA which revealed that sleep quality, as measured by sleep efficiency and percentage of NREM3/4 sleep, was not related to dipping [10]. However, in healthy adults, the percentage of sleep time spent in NREM4 has been shown to predict the degree of both DBP and mean BP dipping after controlling for a number of factors [8].

Patterns of nocturnal dipping can be described through both continuous and categorical methods, the former being the magnitude of the nocturnal BP decline and the latter through separation into dippers and non-dippers [1,2]. The degree of change in PTT and HR from wake to sleep and to all sleep stages in preschool children with SDB was similar to that observed in non-snoring children. Furthermore, the magnitude of change did not differ with SDB severity, suggesting that nocturnal BP patterns are preserved in children with both PS and OSA at the preschool age. These results are in stark contrast to adults with OSA, who exhibit reduced or absent BP dipping [9–14]. Fewer studies have investigated nocturnal dipping in school-aged children with SDB and the effects are less clear. When measured using ambulatory BP, the degree of SBP, DBP and mean BP dipping has been reported to decrease with increasing SDB severity [18,22,23], whilst another study found no differences in the degree of dipping between severity groups [24]. The only study to assess dipping through continuous BP measurement revealed no loss of dipping in school-aged children with SDB [25]. The present study findings support those in older children showing preserved dipping. Considering that BP elevations have been reported at the school age in all severities of SDB during both sleep states [19], but at the preschool age appear to be limited to children with MS OSA during REM sleep [35], overall these findings suggest a progressive impact on the cardiovascular system whereby dipping may be one of the last parameters to be affected. These findings support detection and treatment of OSA in childhood, when the cardiovascular effects are less marked.

Whilst there are many exogenous and endogenous factors that mediate nocturnal dipping [59], the sleep–wake variations in cardiovascular autonomic nervous system activity play a dominant role in 24 h BP variations. Specifically, nocturnal dipping is associated with sympathetic withdrawal and an increase in parasympathetic tone [60]. Adult OSA is associated with profound autonomic dysfunction, involving high levels of sympathetic activity [61]. Surges in night-time BP as a result of obstructive respiratory events [61], in association with other autonomic alterations, such as chemoreflex [62] and baroreflex dysfunction [63], and cardiovascular disease often seen in adult OSA [64], all act to reduce the overall fall in BP during sleep, such that the physiological nocturnal BP decline is reduced with increasing apnoea severity [9,12,14]. However, in our preschool cohort, we found that indices of SDB severity (OAHI, ODI3% and SpO_2 nadir) were not correlated with the degree of nocturnal dipping, as suggested by change in PTT and only weakly related to changes in HR. To reduce the effect of the multiple children who had an OAHI of zero, we separated out preschool children with OSA only and found that nocturnal change in PTT and HR was still not correlated with OAHI, although it was weakly related to oxygenation. Few studies have assessed the determinants of BP dipping in children with SDB and those which have were conducted in school-aged children. Marcus and colleagues found no significant correlation between the indices of OSA severity (obstructive apnoea index and SpO_2 nadir) and the magnitude of the BP dip [53]. By contrast, Amin et al. found the ODI4% to be the best predictor of nocturnal BP dipping [23]. It should be noted that children in our study had less severe OSA than those in the Amin et al. study [23], although our subjects had similar SpO_2 nadirs to those studied by Marcus et al. [53]. Our finding of similar nocturnal changes in PTT, suggesting similar BP dipping between all groups of preschool children, irrespective of SDB severity and snoring status is supported by the overall lack of correlation between indices of SDB severity and nocturnal change in PTT at this age. Nonetheless, we did find some evidence that in preschool children with OSA, the magnitude of oxygen

desaturation may influence the degree of nocturnal change in PTT, suggesting a weak relationship with BP dipping.

The proportion of dippers and non-dippers could not be quantified in the present study, as this traditional categorisation is based upon percentage change in BP [1,2], which is not numerically equivalent to the percentage change in PTT. Instead, we undertook an alternative analysis that identified children with the smallest change in PTT from wake to sleep, suggestive of the smallest nocturnal fall of BP, which represents the children most likely to exhibit autonomic dysfunction and compared the proportion of these children in each group. If each group had the same dipping profile, then it would be expected that equal proportions of children from each group would be in the smallest quartile group for percentage change in PTT. However, we found that a higher proportion of children with MS OSA fell into this quartile compared to the other groups. The lack of statistical significance between groups may reflect a deficit in sample size specific to this analysis. Despite this, we would expect that the loss of dipping would be most likely to occur in those with more severe OSA; hence, perhaps the severity and duration of OSA were not yet enough at the preschool age to make the difference statistically detectable. Nonetheless, as 41% of the MS OSA subjects were in the small dip quartile compared to 23% of the control group, the biological significance of this cannot be discounted. Alternatively, it is plausible that heterogeneity existed within the MS OSA group, with some children having absent dipping, whilst others had exaggerated dipping, which can also occur with autonomic dysfunction [59]. Depending on the study, a pattern of 'non-dipping' has been reported in 48–84% of adults with OSA [11,12]; a prevalence much higher than reported in normal individuals (16%) [65]. Whilst not directly comparable, studies of ambulatory BP in school-aged children with SDB have produced conflicting results, with some studies reporting no group differences in the proportions of non-dippers [24,25,51,52], and other studies finding group differences [18,22]. The absence of dipping exposes tissues and organs to a higher BP for a longer period within each 24 h, resulting in hypertensive damage and thus BP dipping is postulated to be a restorative physiologic process [66]. Given that the loss of nocturnal dipping is known to accelerate the development of cardiovascular disease [3–7], and in adults it has been correlated with target organ damage to the heart [67,68], brain [69] and kidney [70], it is reassuring that our results suggest that preschool children with SDB demonstrate preservation of nocturnal dipping.

We acknowledge that whilst arterial blood vessel stiffness is an important factor in the calculation of PTT, other factors may also influence PTT. Individual differences in vascular compliance and pre-ejection period (the electro-mechanical delay from depolarisation of the left ventricle to aortic valve opening) can lead to variability in PTT between individuals [30,31]. To overcome this, absolute change in PTT from wake to sleep was not compared between individuals, rather the present study compared percentage change in PTT from each individual's own wake value to sleep.

5. Conclusion

Preschool children with SDB experience a significant rise in PTT from wake to sleep, suggestive of a fall in BP, and a nocturnal reduction in HR irrespective of severity and despite increased sleep fragmentation. Unlike adults with SDB, nocturnal dipping appears to be preserved in young children with SDB. The nocturnal reduction in BP is considered a restorative process, and loss of this dip confers significant future cardiovascular risk in adults. As there is evidence that nocturnal dipping is similarly preserved at the school age, present study findings suggest that childhood may be a time when resolution of SDB should be actively pursued, when cardiovascular effects are less marked and before the loss of nocturnal dipping is overtly apparent.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2013.11.787.

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